Life Sciences Enterprise
DuPont Pharmaceuticals Company
REGULATORY AFFAIRS

September 13, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

RE: PROPOSED RULE FOR SUPPLEMENTS AND OTHER CHANGES TO AN APPROVED APPLICATION (DOCKET NO. 99N-0193)

Dear Sir or Madam,

Reference is made to the above-referenced draft rule. Notice of availability of this draft rule, as well as request for comment, was published in the June 28, 1999, edition of the FEDERAL REGISTER.

In response to this request for comments, attached is feedback from the DuPont Pharmaceuticals Company on the content of the draft rule.

We appreciate the opportunity to comment on this draft rule.

Sincerely,

Damaris Degraft-Johnson /JF

Damaris Degraft-Johnson
Senior Director
Worldwide CMC Regulatory Affairs

Attachment

Submitted in Duplicate

99N-0193 C28

PROPOSED RULE FOR SUPPLEMENTS AND OTHER CHANGES TO AN APPROVED APPLICATION

DOCKET NO. 99N-0193 2321 '99 SEP 14 A9:27

GENERAL:

1) We believe the proposal is more burdensome then the current requirements. The proposed rule, as written, increases the number of prior approval supplements required and takes some CBEs and makes them CBE-30s.

2) Throughout the Proposed Rule, there is the phrase "validate the effect of the change" which is defined as "assess the effect of the change". We recommend changing the word "validate" to assess since the application holder must "assess" the effect of the change on the identity, strength, quality, purity, and potency of the drug as the identity, strength, quality, purity, and potency may relate to safety or effectiveness of the drug. We believe this will obviate the potential for confusion arising from the word "validate" which is covered by cGMPs.

3) We believe the Final Rule, when issued, should address more adequately what is meant by major, moderate and minor changes. The guidance, when issued should provide further clarification regarding these changes (including appropriate items to be considered to qualify a change as major, moderate, and minor such as a decision tree), and provide guidance/requirements regarding appropriate testing that should be necessary for each type of submission.

4) We also believe it would be appropriate to ask for Industry assistance (as was requested for the SUPAC Equipment Addendum) in completing both the proposed rule, and the guidance.

5) At times proposed information conflicts with information in other guidelines. We strongly suggest all appropriate guidances be harmonized and combined into one document, or at a minimum, cross-referenced.

SPECIFIC:

Section 314.50(d)(1)(i): We believe the words "particle size" should be removed from the list of examples, unless it is made clear that particle size tests would only be applicable to poorly soluble and insoluble drugs, and other drugs where particle size is likely to impact the identity, strength, quality, purity, and potency of a drug (such as direct compression processes). A suggestion would be "...particle size for poorly soluble or insoluble drugs..."

Section 314.70(a)(2): Again, we believe the word "assess" should be used to replace "validate".

Section 314.70(b): We believe the words "substantial potential" should be described more adequately and defined with specific examples.

Section 314.70(b)(2)(i): We believe the "catch-all" section of the final rule should be the CBE-Zero or CBE-30 section, not the prior approval section.

Section 314.70(b)(2)(iii): We believe the word "significantly" should be added to read "...may significantly affect product sterility assurance". This would add clarification to this statement, as any change has the potential to affect sterility assurance. In addition, examples of what is considered significant should also be included.

Section 314.70(b)(2)(vi):

* We would like clarification on what is meant by "controls drug delivery" such as quantity dispensed, machine calibration, and volume of fill.
* We believe the word "adversely" should be added to read "...may adversely affect the impurity profile of the drug product". Also, please give examples of what would be considered a significant change. One question this section raises is would a change be significant if it were out of profile but within specification.
* We believe the impact on other aspects of the drug should be addressed as appropriate.
* Does this section specifically refer to final packaged product only, or is bulk product included?

Section 314.70(b)(3)(vii): We believe clarification is needed that the test methodologies and validation protocols referred to in this section are for the sterilization process only.

Section 314.70(b)(3)(viii): Please clarify what is meant by "standard operating procedures". According to the current definition of what a "standard operating procedure" is, these are GMP issues and should be handled separately from the submission.

Section 314.70(c): We believe the words "moderate change" and "moderate potential" should be described more adequately, and defined with specific examples.

Section 314.70(d): Again, we believe the words "minor changes" and "minimal potential" should be described more adequately, and defined with specific examples.

Section 314.70(d)(2)(vi): We believe the requirement of "full production batches" is unnecessarily burdensome. If an NDA expiration date may be approved based on pilot

scale batches, then that expiration date should also be able to be extended based on data derived from those pilot scale batches.

Section 314.70(d)(2)(viii): We believe wording should be added to allow for ink printing on modified dosage forms, as this should not impact drug release.

Section 314.70(e): We would like the words "validation studies" to be clarified. Does this mean "assessment studies" to assess the impact of the change; or does is refer to GMP validation studies? If this refers to GMP validation studies, we believe this should only be applicable for sterility validation (i.e. filing issue). Other validation studies are adequately covered by cGMPs.

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